Exacerbation Rate Reduction With Mepolizumab Stratified by Maintenance Oral Corticosteroids Use and Eosinophil Levels: A Post Hoc Analysis of the DREAM and MENSA Studies

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Treatment of severe asthma is often complex owing to marked disease burden, leading 30%-40% of patients to require maintenance oral corticosteroids (OCS). Several recently approved biologic therapies for severe asthma enable an appropriate corticosteroid-sparing strategy when added to standard of care. Mepolizumab is a humanized monoclonal antibody against IL-5 licensed for the treatment of severe eosinophilic asthma (SEA) [1,2].

The benefit of mepolizumab in reducing the frequency of exacerbations and the dose of OCS has been proven in randomized controlled clinical trials and, more recently, in real-life studies [2].

Specifically, findings from 2 large placebo-controlled trials in the clinical development program of mepolizumab (DREAM, NCT01000506 [1] and MENSA, NCT01691521) [3] have shown clinically significant reductions in asthma exacerbation rates after treatment with mepolizumab in patients with SEA. Furthermore, the clinical benefit of mepolizumab in reducing oral corticosteroid doses was demonstrated in the SIRIUS OCS-sparing study (Oral Glucocorticoid-Sparing Effect of Mepolizumab in Eosinophilic Asthma Study) [4]. Modelling analysis in the DREAM study identified blood eosinophil count as a predictor of response to mepolizumab; hence, patients with severe asthma in the subsequent MENSA study were selected based on their blood eosinophil count to fulfil the eosinophilic phenotype criterion.

The search for new biomarkers of early response to biologics in severe asthma is ongoing, and in some studies, the use of maintenance OCS has been proposed as a potential predictor of response. In a recent post hoc analysis by Bleecker et al [5], the OCS maintenance dose predicted the efficacy of benralizumab in terms of fewer exacerbations and improved FEV_1. However, the influence of OCS on blood eosinophil levels is well-known, and their use as maintenance treatment makes it difficult to establish a common threshold to define eosinophilia. Consequently, we believe it is necessary to evaluate the efficacy of biological therapies in relation to OCS use and to blood eosinophil levels [6].

We assessed the role of maintenance OCS in reducing the exacerbation rate with mepolizumab in patients with SEA stratified by baseline blood eosinophil levels.

We performed a post hoc analysis using exacerbation data from the DREAM study (N=616; mepolizumab at 75 mg IV, 250 mg IV, and 750 mg IV) and the MENSA study (N=576; mepolizumab at 75 mg IV and 100 mg SC), in which baseline maintenance OCS were taken by 188 (31%) and 144 (25%) patients, respectively. Baseline data on eosinophil levels and use of maintenance OCS were necessary for patients to be included in this post hoc analysis. Patients were excluded if they had baseline blood eosinophil levels <150/μL.

Patients were divided into 8 groups according to their baseline eosinophil levels (cells/μL) on the one hand (≥150-300, ≥300-500, ≥500, all patients, ie, 4 groups) and according to OCS maintenance use (yes/no) on the other (Table).

In order to model the response variable due to the dispersion of the data, the exacerbation rates were analyzed using a negative binomial regression model (SAS). Explanatory covariates included treatment group, exacerbations in the year prior to the study (as an ordinal variable), baseline FEV_1, study, region, and logarithm of time on treatment as an offset variable. This model was fitted for the 8 subgroups based on the baseline eosinophil levels and the baseline maintenance OCS (see above).

Of the 1192 patients included in the DREAM and MENSA studies, 920 had blood eosinophil levels ≥150/μL (analysis population) and were eventually included in this post hoc analysis; 278 received placebo and 642 mepolizumab.

Demographic characteristics were similar in both studies and in the analysis population. Exacerbation rate reductions with mepolizumab were similar between OCS-treated patients (n=243) and patients who did not receive OCS (n=677). The results show greater reductions at higher baseline eosinophil counts (groups 3>2>1, and groups 7>6>5, respectively) (Table), which were maintained in both the total and disaggregated analyses. The role of mepolizumab in reducing the number of exacerbations seems not to be affected by baseline OCS treatment (the ratios in groups 4 and 8 are similar).

Table. Annual Exacerbation Rates According to Baseline OCS Use Stratified by Baseline Blood Eosinophil Levels

Baseline maintenance OCS	Baseline blood eosinophil count	150-300/µL	300-500/µL	≥500/µL	All
Yes	n=243 (groups 1-4) (Placebo /Mepolizumab)	1. 20/56	2. 18/50	3.33/66	4.71/172
	Annual exacerbation rate				
	Placebo	2.57	2.30	3.11	2.84
	Mepolizumab	1.57	1.26	0.99	1.29
	Rate ratio	0.59	0.55	0.32	0.45
	Mepolizumab/Placebo 95% CI	(0.31-1.11)	(0.29-1.05)	(0.20-0.51)	(0.33-0.63)
No	n= 677 (groups 5-8) (Placebo/Mepolizumab)	5.66/168	6.58/130	7.83/172	8.207/470
	Annual exacerbation rate				
	Placebo	1.04	1.45	2.25	1.65
	Mepolizumab	0.77	0.99	0.66	0.81
	Rate ratio	0.72	0.68	0.30	0.49
	Mepolizumab/Placebo 95% CI	(0.42-1.22)	(0.44-1.05)	(0.21-0.42)	(0.38-0.63)
All	n= 920 (Placebo/Mepolizumab)	86/224	76/180	116/238	278/642
	Annual exacerbation rate	Placebo	1.41	1.64	2.49 1.94
	Mepolizumab	0.95	1.06	0.75	0.92
	Rate ratio	0.67	0.64	0.30	0.48
	Mepolizumab/Placebo 95% CI	(0.45-1.01)	(0.45-0.92)	(0.23-0.40)	(0.39-0.58)

Abbreviations: OCS, oral corticosteroid.

Several studies have evaluated the influence of OCS maintenance use on the clinical benefit of mepolizumab in terms of reducing exacerbations [7,8]. One of these was conducted using data from MENSA and from the MUSCA study and assessed the annual rate of clinically significant exacerbations in patients receiving mepolizumab 100 mg SC or placebo according to the use of maintenance OCS [8].

The results of these studies are consistent with ours and reveal that previous maintenance OCS have no effect on reduction of the exacerbation rate with mepolizumab. Nonetheless, the higher eosinophil levels are associated with a better response to mepolizumab in the form of a reduction in the exacerbation rate [9], as reported for other biologics [10].

The present study did not aim to evaluate the capacity of mepolizumab to reduce or suspend OCS, which was previously demonstrated in the SIRIUS study [4]. Moreover, the response to a biologic is based on improvement in parameters other than exacerbations, which were not analyzed here. Nonetheless, exacerbations are one of the most relevant criteria when evaluating drug efficacy in severe asthma. When considering biological options for corticosteroid-dependent asthmatics, the fact that OCS-dependent patients respond as well to mepolizumab as non–OCS-dependent patients in terms of a reduced exacerbation rate constitutes an advantage of mepolizumab.

Several aspects of our study require further discussion. We performed a post hoc analysis in which the sample size of each group was small. A randomized study with a sufficiently large sample to assess the endpoint of interest would be required to obtain more conclusive results and thus minimize the possibility of false positives and false negatives.

The effect of maintenance OCS on blood eosinophil levels is well documented. Our post hoc analysis indicates that, in corticosteroid-dependent patients, the benefit of mepolizumab in terms of reducing exacerbations seems not to be influenced by previous maintenance OCS. However, our results should be interpreted with caution considering the small sample size.

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Conflicts of Interest

MG Sánchez-Herrero, S Joksaite, and D Bañas are employees of GSK. A de Andrés was an employee of GSK at the time this analysis was conducted. The remaining authors declare that they have no conflicts of interest.

Previous Presentations

This work was presented as a poster during the ISAF Congress, Madrid, November 2018.

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